Hyland Immuno

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Baxter 9225 '00 AUG 31 P5:13

28 August 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rm 1061
Rockville, MD 20852

Subject: Comments to Docket Number 00D-1318, Guidance for Industry, Chronic Cutaneous Ulcer and Burn Wounds-Developing Products for Treatment, June 28, FR Doc –00-16394)

Dear Sir/Madam,

Baxter Healthcare Corporation, Hyland Immuno is submitting the following comments to the FDA in regards to the referenced draft guidance document.

Part II, Claims:

II.A, General Considerations, General comment: We believe that wound healing trajectories should be considered as an alternative endpoint for wound healing trials as discussed by Robson, M, et. al., Arch Surg, 2000; 135:773-777. As described in this paper, trajectories provide detailed information about agent effectiveness over the entire span of wound healing.

II A, General Considerations, Page 1, first paragraph of this section: The opening paragraph refers to claims of beneficial effects for separate types of wounds for which the product is intended. Safety data should also be addressed.

Footnote No. 2, page 1: We do not understand the meaning of footnote #2. Any product, medical device, drug, or biological that seeks an indication for wound healing, by definition would require clinical study in order to prove safety and efficacy of the product for that purpose.

II.B. Claims related to improved wound healing/1. Incidence of complete wound closure, page 2: We would like FDA to clarify how wound closure would be defined in skin graft/burn trials in this section.

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Cross-referencing page 14: The discussion of "standard of care considerations for burns" on page 14, although it mentions wound closure, does not define wound closure as it relates to skin grafts. This needs to be addressed.

II.C. Other Considerations Related to Improved Wound Care, Page 5, Section 2, Debridement: We would like to have a more clear and complete definition of what comprises "full and thorough" debridement for each indication that would be acceptable to FDA. Furthermore, how can new methods be validated without conducting clinical trials on such methods? Would FDA accept methods if they are validated by performing *in vitro* or animal studies? Please clarify. Would FDA accept a test validation method if it is described in a peer-reviewed journal article and, if so, we request that it be stated explicitly in the acceptance criteria?

Part III, Preclinical Considerations:

Page 5, first sentence of this section, at bottom of page: Add word in *italics*: This section consists of specific points to consider for wound indication drugs, *devices,* and biological products.

III.A. Animal Models for Wounds, page 6: Please include in this section an explicit statement that any new animal model is acceptable as a test method if the method is validated.

III.B. Biodistribution and Pharmacokinetic Studies, page 6, last sentence which begins *"Where feasible"*: We would like to see an explanation of what situations would make it "feasible" to provide the type of data requested.

III.C, Toxicity Studies, page 7, paragraph 1, last sentence, delete as indicated: "Vehicle and sham controls should be employed where appropriate, to evaluate any adverse effects of product formulation components ~~on wound healing.~~ "

Comment: The words "on wound healing" are deleted because an effectiveness evaluation is not appropriate in a toxicity evaluation of a product.

Part IV. Clinical Trial Considerations:

IV. A. Absorption Studies, page 8: We are concerned about the potential to make accurate systemic measurements of the presence of a biologic substance or its degradation product (i.e. fibrin sealant) that has not been introduced intravenously. Attempts to measure the presence of such substances in wound bed tissue would require biopsy of tissue for analysis that would not likely be permitted by an IRB. Tests will have to be devised to distinguish one human fibrin from that of another human fibrin (i.e., fibrin sealant). Measurement of an incremental increase in the systemic circulating level of a biologic that already has a counterpart, such as fibrin sealant, will be impractical and probably immeasurable. In part, it must be considered that absorption by macrophages at the wound site will most likely account for primary removal of material from the wound bed. In addition, the ability to measure some quantity of fibrin sealant or its degradation product, and distinguish it from the fibrin formed by the patient and present in his/her serum, will also be impractical.

The guideline should distinguish between a drug substance which can elicit a biological response at concentrations significantly below their application level from a biologic which would be entirely masked by the presence of normally occurring analygous substances.

IV. C. Assessment/Quantification, Page 9, Paragraph 1, line 3: Add text in *italics*: "...if photographs are to be used for measurement and documentation, the lighting, *distance/objective*, and type of camera should be specified".

IV. C. Assessment/Quantification, Page 9, Paragraph 1, last line: Add the following sentences in *italics*: "Proposals for novel assessment systems should include validation data. *With validation data in place, the data can be accepted. Examples of validation include the following [give examples]*:

> Comment: We are concerned about an assessment system being accepted toward licensure, and would like to see more examples of validated systems so that there is assurance that they support licensure.

IV. C.2, Wound Size, Paragraph 1, line 6: Change wording to the italics: "For ulcers that extend deeply into tissue, *depth* ~~volume~~ or surface area should be measured when feasible."

> Comment: We are concerned that there is really no way to accurately and quantitatively measure depth with a validated method. However, it would be even more difficult to measure volume. We do not believe that under sterile conditions the volume of an injury such as an ulcer can be assessed, and that depth is a more feasible and relevant measurement.

IV. C.2 Wound Size, Page 10, line 5: Change sentence wording to *italics*: "Validated test methods for determining burn depth do not exist currently, but biopsy and Doppler measurement of blood flow ~~are sometimes used~~ *can be used.*

IV. C.2, Wound Size, Page 10, Paragraph 1, line 7: Delete the last 2 sentences of paragraph 1 beginning "Wound depth heterogeneity is often an impediment to quantitative measures...ultimately grafted.

> Comment: We would like to have a further understanding of the intent of these statements. Is the emphasis to distinguish between partial and full thickness wounds or is this meant to state a requirement for real measurement of each wound? The sentence addressing wound depth heterogeneity is not clear and restates what was already said in the previous sentences. The last sentence of the paragraph beginning with "Initial clinical assessment of full thickness wounds..." is not clear and requires qualification as to why this is to be done.

IV. D.1, Population, Chronic Cutaneous Ulcers, 11, 2nd paragraph at top of page: Please omit the last sentence beginning "However, if demonstration of efficacy is limited to ...may be similarly limited". This statement is not meaningful and is extremely limiting. This is because ulcers come in different shapes and sizes and the outcome cannot be limited to the size of the ulcer being tested.

We appreciate your consideration of our comments. If there are any questions, please contact me at 818-507-5523.

Sincerely,

Arlene Vidor
Vice President, Global Regulatory Affairs
Wound Management

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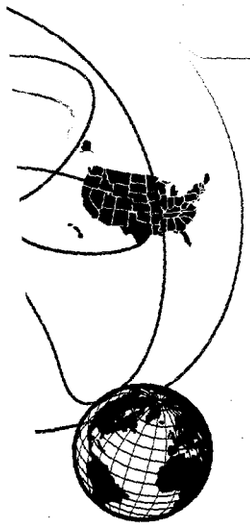

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